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Mesenchymal stem cells as carriers for systemic delivery of oncolytic viruses

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ABSTRACT

Progress in genetic engineering led to the emergence of some viruses as potent anticancer therapeutics. These oncolytic viruses combine self-amplification with dual antitumor action: oncolytic (destruction of cancer cells) and immunostimulatory (eliciting acquired antitumor response against cancer epitopes). As any other viruses, they trigger antiviral response upon systemic administration.

Mesenchymal stem cells are immature cells capable of self-renewing and differentiating into many cell types that belong to three germinal layers. Due to their inherent tumor tropism mesenchymal stem cells loaded with oncolytic virus can improve delivery of the therapeutic cargo to cancer sites. Shielding of oncolytic viral construct from antiviral host immune response makes these cells prospective delivery vehicles to even hard-to-reach metastatic neoplastic foci.

Use of mesenchymal stem cells has been criticized by some investigators as limiting proliferative abilities of primary cells and increasing the risk of malignant transformation, as well as attenuating therapeutic responses. However, majority of preclinical studies indicate safety and efficacy of mesenchymal stem cells used as carriers of oncolytic viruses. In view of contradictory postulates, the debate continues.

The review discusses mesenchymal stem cells as carriers for delivery of genetically engineered oncolytic constructs and focuses on systemic approach to oncoviral treatment of some deadly neoplasms.

1. Introduction

Despite unquestionable progress in cancer treatment, several malignancies still tend to elude successful cure or medically-induced remission. Continued rise in morbidity in the last twenty years for gliomas, melanoma or pancreatic cancer makes them a major public health concern and a research challenge. Although radically improved outcomes might be unattainable yet, stepwise progress is likely with novel or improved treatments involving immunotherapy, cell-based therapeutics, oncolytic virotherapy and hybrid approaches.

Intriguing recoveries from cancer following natural viral infection (e.g. measles) have been known to medicine since early 20th century but this early lead based on use of wild-type adenovirus, poliovirus or Coxsackie virus was marred by virus-associated morbidity and complications and was later abandoned (Kelly and Russell, 2007). Clinical utility of oncolytic viruses has been steadily regaining ground since the latter part of the 20th century with advances in genetic engineering. Current generation of many oncolytic viral constructs allows targeting and destroying cancer cells while toxicities to surrounding normal tissues are minimized.

A concurrent development in cell-based anticancer therapies has led to the concept of oncoviral viruses' delivery to tumors *via* cellular carriers. It assumes that certain types of cells pre-loaded *ex vivo* with some curative cargo can be administered systemically, delivered to and released in target tissues.

This review highlights therapeutic use of mesenchymal stem cells (MSCs) preloaded *ex vivo* with oncolytic viral cargo to deliver the virus to tumor foci following reinfusion into bloodstream (Fig. 1). This "Trojan horse" approach fits well with carrier cells that possess natural tropism or are targetable to disseminated/metastatic tumor beds.

2. Mesenchymal stem cells: an overview

2.1. Origin, phenotype and differentiation

Friedenstein and colleagues identified in the 1970s a subpopulation of non-hematopoietic cells in bone marrow with morphology akin to that of fibroblasts; these cells were able to form colonies *in vitro*, and

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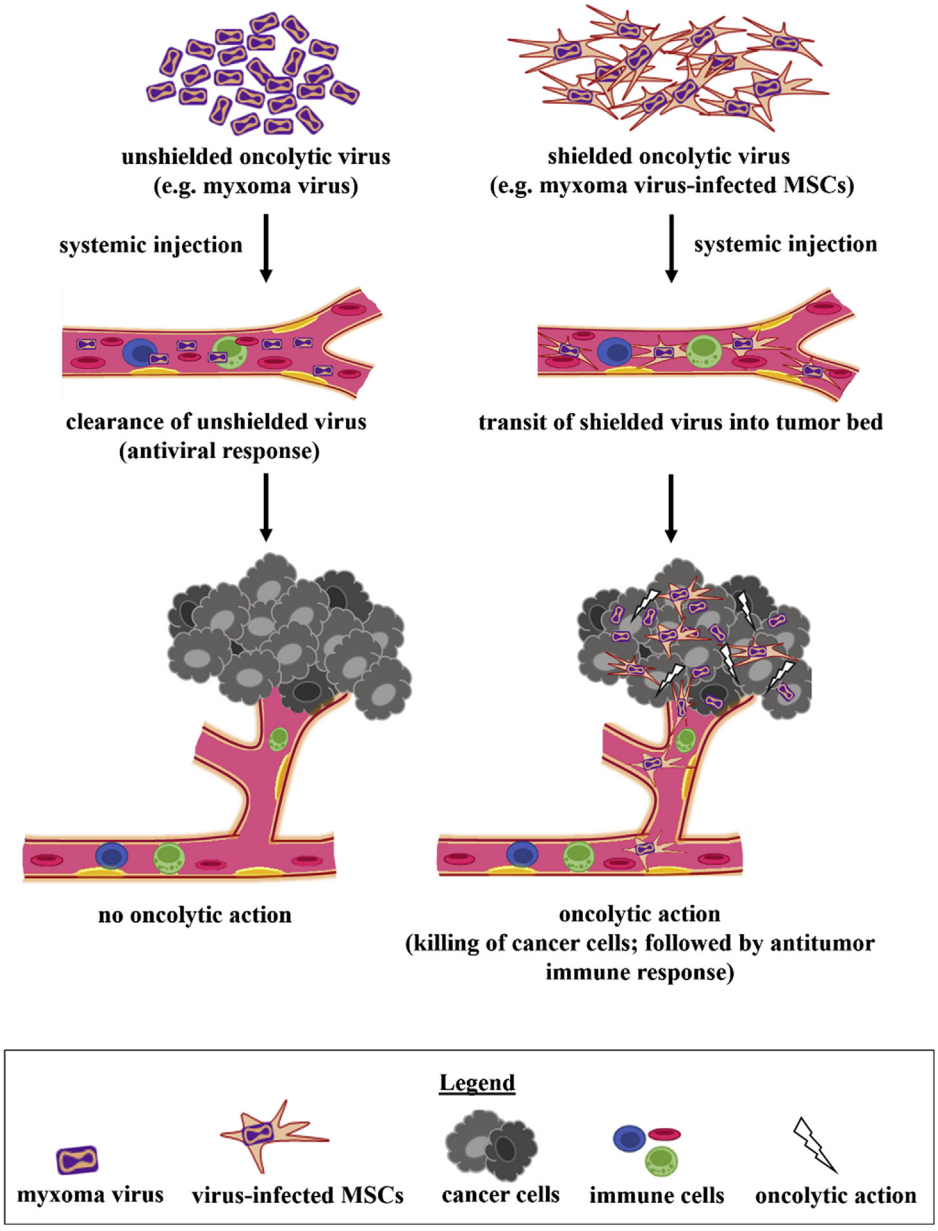

Fig. 1. Advantage of systemic administration of oncolytic virus shielded by MSCs. Unshielded oncolytic virus (e.g. myxoma virus), when administered intravenously, elicits antiviral response (NK cells, cytokines, mononuclear phagocyte system (MPS), complement activation) leading to virus clearance thus no oncolytic action. On the contrary, shielding of viruses by suitable protective carrier e.g. mesenchymal stem cells (MSCs) allows effective delivery to tumor bed and oncolytic action. Use of the therapeutic system ("Trojan horse") i.e. MSCs infected with oncolytic virus enhances oncolysis and boosts acquired immune response augmenting overall antitumor effect.

came to be known as CFU-F (colony forming unit-fibroblastoid) cells (Friedenstein et al., 1976). Because of their ability to renew and differentiate, these multipotent stromal cells derived from bone marrow were agreed upon as stem cells and dubbed mesenchymal stem cells (MSCs). MSCs occurring in bone marrow constitute a heterogeneous population that comprises a mixture of hematopoietic progenitors originating from mesoderm and constituting only a small percentage of self-renewing stem cells (Uccelli et al., 2008). In 2005 and 2006, ISCT (International Society for Cellular Therapy) recommended replacing the term "stem" with "stromal" and considering candidate cells as MSCs only if they could demonstrate solely adherent replication and presented (or lacked) the following surface antigens: $CD73^+$, $CD90^+$, CD105+, $CD14^-$, $CD34^-$, $CD45^-$ CD11b-, $CD19^-$ and CD79α-, together with the ability to differentiate into osseous, cartilage and adipose cells. MSCs also express low level of major histocompatibility complex (MHC) class I molecules and do not express MHC class II on the cell surface, rendering allogeneic transplants feasible. Despite the ISCT recommendation, the term "stem" still remains in general common use to define MSCs (Dominici et al., 2006; Lv et al., 2014).

MSCs derived from various tissues share common features but they can vary in their differentiation and angiogenic properties. Bone marrow and adipose tissues are the main common sources of MSCs (called BM-MSCs and ADSCs, respectively), chiefly due to the ease of material collection, but MSCs can also be isolated from e.g. umbilical cord blood, menstrual blood, Wharton's jelly, placenta and several other tissues. Lv et al. have demonstrated that only a small fraction of the cells in isolated MSC populations are genuine stem cells with potential for *bona fide* three-dimensional differentiation. They also proposed other specific markers to stress the stemness of MSCs, including Stro-1, SSEA-4 and CD146 (Lv et al., 2014). Significant differences were claimed between MSCs derived from newborn and adult tissues, with the former showing less differentiation and higher survival potential (Hass et al., 2011). A specific marker was recognized with respect to MSCs source: CD271 was recommended to be used when characterizing MSCs derived from bone marrow (Álvarez-Viejo et al., 2015).

Rather unsurprisingly, MSCs isolated from other species do not have the same phenotype as those of human origin. It is generally accepted that all MSCs lack CD45, a hematopoietic marker, as well as CD31, an endothelial marker. Variations in surface antigen expression can in addition result from factors released by helper cells at the initial stages

of subculture. Also, *in vitro* expression of certain MSC markers is not always concordant with their *in vivo* expression (Nery et al., 2013; Lv et al., 2014).

2.2. Collection and safety

MSCs isolated from adult tissues can help resolving some ethical issues raised with use of stem cells. From the economic perspective, clinical applications of ADSCs seem advantageous to BM-MSCs due to higher (several hundred-fold) intrinsic yield; adipose tissue is also more abundant and more easily accessed, for example during liposuction. In some cases, however, clinical benefits of BM-MSCs might prevail if particular cell populations are used (Strioga et al., 2012).

Clinical use of MSCs requires rather large quantities of these cells, which translates into extensive *in vitro* cell culture (Wang et al., 2012). Cases of documented genomic instability of isolated stem cells were reported, together with acquiescence of neoplastic features; since this might affect tumor proliferation it would also be a problem for anti-cancer therapies based on MSCs (Hanahan and Weinberg, 2011; Kim and Park, 2017). BM-MSCs were also reported to acquire chromosomal aberrations and undergo spontaneous transformation during long *in vitro* culture, resulting in tumor formation *in vivo* (Wang et al., 2005).

Both preclinical and clinical data seem to indicate the safety of using BM-MSCs and ADSCs. The vast majority of small-sized clinical trials conducted with MSCs in regenerative medicine applications has not reported any major health concerns, suggesting that MSCs-mediated therapies are relatively safe (Herberts et al., 2011; Lukomska et al., 2019). Biological activities such as proliferation and multipotency of human adipose-derived adult stem cells (as opposed to embryonic ones) were not clearly affected by wild-type reovirus challenge as evidenced by survival, osteogenic and adipogenic differentiation potential assays following treatment with this onolytic reoviruses (Park and Kim, 2017). In the context of MSCs used solely as carriers of oncolytic constructs the dimension of the safety issue could thus be somewhat less stringent. The results support clinical use of human adipose-derived stem cells as an effective cell carrier of oncolytic reovirus to maximize their tumor tropism and anti-tumor activity. The concerns about the purported ability to promote tumor growth and metastasis and overestimated therapeutic potential of MSCs pertain rather to the field of regenerative medicine (Volarevic et al., 2018). Nonetheless, in view of many contradictory postulates, the debate continues concerning safety of using MSCs in anticancer research and in clinical setting (Sensebé et al., 2012; Kundrotas et al., 2016).

Four clinical trials using oncolytic virus-infected MSCs were undertaken to date. All were/have been phase I studies. Three of them have used BM MSCs and adenovirus and one study used ADSCs and measles virus; their details can be found in Table 2.

2.3. Tissue tropism

Several studies have shown that injected MSCs are capable of migrating directionally (homing) to specific tissues, including injury and tumor sites. Migration of MSCs towards tumor bed is triggered by a signaling cascade similar to that in wounds that do not heal (Dvorak, 1986). In addition to MSC-intrinsic factors (cell culture conditions, cell population heterogeneity, expression of migratory molecules), the tropism of MSCs towards cancerous tissues is affected by tumor site-intrinsic properties such as oxygenation status, degree of vascularization, inflammatory status, etc. (Najar et al., 2016).

Several types of molecules affecting MSCs migratory behavior have been identified. They include growth factors and their receptors, e.g. epidermal growth factor (EGF), vascular endothelial growth factor A (VEGF-A), fibroblast growth factor (FGF), platelet derived growth factor-AB (PDGF-AB), hepatocyte growth factor (HGF), transforming growth factor β1 (TGF- β1) or insulin-like growth factor 1 (IGF- 1); cytokines such as tumor necrosis factor α (TNF-α), Interleukin 6 (IL-6) and Interleukin 8 (IL-8); chemokines e.g. CXCL-12 (C-X-C Motif Chemokine Ligand 12), CCL-2 (C–C Motif Chemokine Ligand 2), CCL-3 (C–C Motif Chemokine Ligand 3) and their receptors, for example CCR4 (C–C Motif Chemokine Receptor 4) or CXCR4 (C-X-C Motif Chemokine Receptor 4); also vascular cell and intercellular adhesion molecules (VCAM and ICAM, respectively) have been implicated (Musiał-Wysocka et al., 2019).

Tissue homing of MSCs following systemic injection results from interactions between their surface proteins (such as integrins) with blood vasculature components and target site-specific receptors or adhesion molecules, including extracellular matrix (ECM) proteins such as collagen, fibronectin or laminin.

Migratory patterns of MSCs largely depend on various cytokine / receptor pairs such as SDF-1 (stromal cell-derived factor 1) / CXCR4, SCF (stem cell factor) / c-Kit (tyrosine kinase receptor), HGF / c-Met (hepatocyte growth factor receptor or HGFR), VEGF / VEGFR (vascular endothelial growth factor receptors), PDGF / PDGFR (platelet derived growth factor receptor), MCP-1 (Monocyte chemoattractant protein-1) / CCR2 (C–C Motif Chemokine Receptor 2) and HMGB1 (high-mobility group protein 1) / RAGE (receptor for advanced glycosylation end) (Momin et al., 2010; Shah, 2014).

Among these cytokine/receptor pairs the SDF-1 factor and its receptor CXC-4 (CXCR4) are important mediators of stem cell recruitment to tumors (Suárez-Álvarez et al., 2012). It was demonstrated that expression of CXCR4 is turned off during cell culture (Phinney and Prockop, 2007), but induction of cytokines (HGF, IL-6), under-oxygenation conditions or its direct introduction *via* viral vectors restores its expression (Bobis-Wozowicz et al., 2011).

Other important signaling pathways, affecting survival and stability of MSCs, include PI3K (Chen et al., 2013), urokinase-type plasminogen activator receptor (Gutova et al., 2008; Vallabhaneni et al., 2011) and proteinase activated MMP1 receptor 1 (Ho et al., 2009).

Effective MSCs migration was demonstrated e.g. into glioma (Smith et al., 2015), breast cancer (Ma et al., 2015) and liver cancer (Xie et al., 2017). Tissue tropism confers MSCs with significant potential to advance anticancer treatment since it makes these delivery vehicles particularly attractive for targeting various therapeutic agents. For example natural tropism to tumors shown by MSCs adds to better spread of viruses if MSC-derived progeny particles can be produced *in situ* (Koks et al., 2015).

2.4. Immunological properties

Immunological properties of MSCs affect significantly their therapeutic potential. Low immunogenicity of allogeneic MSCs allows them to avoid recognition and adverse immune response. Lack of co-stimulatory molecules expression and ensuing low immunogenicity of MSCs results in no need for immunosuppression during allogenic transplantation (Chulpanova et al., 2018a,b). However, MSCs perhaps should not be considered truly immunologically privileged (at least not to the extent claimed) but rather “immune evasive” as they could elicit a humoral and cellular immune response *in vivo* (Ankrum et al., 2014). These authors suggested also various strategies to protect MSCs from immune detection and to prolong their persistence *in vivo* by engineering MSC expression of immunosuppressive and immunoevasive factors.

Little is still known about cellular components affecting immunogenicity of MSCs but the mechanisms of MSCs immunomodulation (release of soluble factors, anergy, apoptosis induction) appear to be coordinated with homeostatic functioning of the immune system *via* a complex network of expression and cytokine responses (English, 2013). Immunomodulation of MSCs by activated cells of the immune system is brought about by released proinflammatory cytokines and is mediated by adhesion molecules (integrins) expressed on MSCs surface (Wang et al., 2015). Depending on kind and concentration of these cytokines, the immunomodulatory effects differ, revealing inherent

plasticity profiles of MSCs. Sizeable variability of such effects has also been linked to donor source (Mattar and Bieback, 2015). micro-environment. Evidence is now emerging that there exist a cross-talk between MSCs and the status of local microenvironment. The latter appears to be key in making MSCs immunosuppressive. It is clear that MSCs can also modulate both innate and adaptive responses. Even though MSCs themselves do not directly influence the immune system they are capable of "re-educating" immune cells. Expression of numerous integrin family receptors, as well as various adhesion molecules, allows MSCs to interact with immune cells. This leads to generation of regulatory T lymphocytes (Treg) and B lymphocytes (Breg), as well as antigen-presenting cells (APCs) and natural killer cells (NKs). Such upregulation contributes to tolerogenic tumor environment and ultimately results in immune tolerance; it is interleukin-10 (IL-10) released by these cells that plays the central role in multiple-pathway immunomodulation exerted by MSCs (Franquesa et al., 2012; Ribeiro et al., 2013; Najar et al., 2016).

To obtain a balanced therapeutic effect when using oncolytic viruses in combination with MSCs, the expression (under conditions mimicking physiological settings) of MSC-related immunogenic and immunosuppressive factors needs to be taken under consideration, along with expression of therapeutic susceptibility biomarkers (Josiah et al., 2010; Sensebé and Fleury-Cappellesso, 2013; Aurelian, 2016). The immunosuppressive features of MSCs, together with active shielding of the viral cargo from immune system surveillance add to the prevention of inflammatory processes accompanying virotherapy and boost destructive power of oncolytic viruses.

2.5. Pro- and anti-cancer properties

The mechanisms underlying the relationship between MSCs and immune cells in the tumor microenvironment are not fully understood and remain a field of active research in order to gain a more coherent picture of these interactions (Rivera-Cruz et al., 2017; Lin et al., 2019). Studies have claimed MSCs to promote (e.g. in breast and colon cancers) or to inhibit (e.g. in liver, lung and pancreatic cancer) tumor progression and metastasis using various mechanisms, mainly by release of soluble factors that activate or inhibit innate and adaptive immune responses (e.g. Yulyana et al., 2015; Lin et al., 2016; Zhong et al., 2017), stimulate or inhibit angiogenesis and maintenance of cancer stem cell niche (Lin et al., 2019).

On the one hand, following accumulation of MSCs in sites of tumor growth they differentiate into pericytes or tumor-associated fibroblasts (TAF) and can co-form a growth-enhancing microenvironment (Musiał-Wysocka et al., 2019). Some researchers claim that MSCs can support malignant transformation, establishment and maintenance of cancer cells, promotion of angiogenesis and neovascularization-sustaining neoplastic tissues, metastasis formation and chemoresistance to drugs (Nwabo Kamdje et al., 2017) and releasing cytokines such as vascular endothelial growth factor (VEGF), interleukin-6 and 8 (IL-6 and IL-8), transforming growth factor β (TGF-β), epithelial growth factor (EGF) and platelet-derived growth factor (PDGF) (Chulpanova et al., 2018a). On the contrary, MSCs infected with oncolytic viruses do not seem to exert any of these protumorigenic effects (see Table 2). This does not contradict tumor microenvironment triggering plasticity mechanisms in MSCs, so that they contribute to the formation of cancer stem cell niche and support stemness (Nwabo Kamdje et al., 2017).

On the other hand, the unique tropism of native and modified MSCs towards inflammatory tissues continues to be exploited by novel anti-cancer strategies. Some researchers who tested unmodified MSCs have stressed their anti-cancer properties (Chanda et al., 2009; Abd-Allah et al., 2014; Nasuno et al., 2014). MSCs are believed to inhibit tumor growth by arresting cell cycle, suppressing proliferation, blocking PI3K/AKT pathway and expressing suppressor genes (Chulpanova et al., 2018 a). Unmodified MSCs were shown to exert antineoplastic effect both *in vitro* and in various animal tumor models; this was ascribed to MSCs-released factors dampening proliferation of glioma, breast cancer and liver cancer cells (Ho et al., 2013; Xie et al., 2013; Leng et al., 2014; Wu et al., 2016a,b). Correct karyotype and no malignant transformation *in vivo* were reported for BM-MSCs (Kim et al., 2009; Jones et al., 2013) while chromosomal instability may just reflect cell ageing (Tarte et al., 2010). The latter, resulting in irreversible halt of cell growth, is a problem, however, when propagating MSCs (Ohtani and Hara, 2013). It limits proliferative capabilities of primary cells (Shvarts et al., 2002), attenuates therapeutic potential (Sepúlveda et al., 2014) and increases the risk of malignant transformation (Shay and Roninson, 2004; Gosselin et al., 2009).

Akimoto et al. (2013) reported that MSCs derived from different tissues could either stimulate or dampen the proliferation of glioma cells. In addition, MSCs from the same source and cultured *in vitro,* promoted or inhibited tumor formation depending on the administration mode used (Jazedje et al., 2015). Intravenous injection of BM-MSCs, conversely, repressed tumor growth in a murine Kaposi's sarcoma model (Khakoo et al., 2006). Such contradictory results have been noted both *in vitro* and *in vivo* for various types of tumors as well as for tumor cell lines (Wu et al., 2016a,b; Larmonier et al., 2003). Similar to BM-MSCs, MSCs from adipose tissue (ADSCs) also exhibit dual (pro- and anti-cancer) properties; this was reported for breast cancer (Kucerova et al., 2015) and prostate cancer (Cavarretta et al., 2010). Since conflicting reports have been published concerning therapeutic use of ageing MSCs it should be borne in mind that this type of cell favors migration and proliferation of cancer cells *via* galectin secretion (ADSCs) (Li et al., 2015) or *via* secretion of IL-6 in the case of umbilical cord-derived MSCs (UC-MSCs) (Di et al., 2014). However, when these UC-MSCs with pro-tumoral properties were initially treated with IL-6, they started to exert anti-tumoral effects (Wang et al., 2015). On the contrary, it was demonstrated that ageing ADSCs inhibited tumor growth but when they were stimulated by cancer cells their therapeutic benefits vanished (Özcan et al., 2015). Also, ageing BM-MSCs were reported to induce ageing of adjacent proliferating MSCs (Severino et al., 2013).

3. Engineered MSCs

Despite low immunogenicity MSCs are believed not to persist for long following systemic administration; therefore viral and non-viral engineering strategies have been employed to protect MSCs from immune detection and induce immunoevasive factors. They include forced expression of decoy or inhibitory receptors through covalent conjugation chemistry or through insertion of antibody fusion proteins into the cell membrane *via* palmitated protein G (PPG); increased persistence can also be achieved through using immunoevasins or sustained release of immunosuppressive factors (Ankrum et al., 2014).

MSCs have been successfully engineered to express various therapeutic agents: small chemicals such as paclitaxel or cisplatin (Lin et al., 2019), proapoptotic and suicide genes (Mueller et al., 2011; Altaner et al., 2014), anti-angiogenesis factors (Chu et al., 2014) and immunomodulatory cytokines like interleukin-12, tumor necrosis factor (TNF) α, interferons β and γ (Ryu et al., 2011; Shahrokhi et al., 2014; Zhang et al., 2015).

Some neoplasms may be deficient or downregulated in specific miRNAs therefore exosomes, which contain a variety of miRNAs, or which can be enriched in them, can transfer such cargo to cancer cells. MSCs, or rather exosomes derived from MSCs, can be thus used as carriers for such therapeutic miRNAs. However, in view of somewhat discordant results of this approach it has been postulated that MSCs should first be engineered in order to obtain stable expression of some cancer killer genes before exosomes' isolation (Lin et al., 2019). MSCs engineering has created new prospects for combinations of MSC-based cell therapies with other therapeutic modalities, e.g. immune checkpoint blockade (Conry et al., 2018), nanotherapeutics (Lawler et al., 2017; Garofalo et al., 2018; Kalimuthu et al., 2018). These, and other

therapeutic approaches have been extensively described elsewhere (e.g. Bitsika et al., 2013; Chulpanova et al., 2018 a). Some of these studies have advanced from preclinical to phase I/II clinical trials; however, cell-based therapies have a number of potential disadvantages mediated by the properties of cells (Chulpanova et al., 2018 b).

4. Engineered oncolytic viruses

The renewed interest in clinical development of oncolytic viruses is in part the result of genetically modified viral constructs that can confer increased tissue specificity and initiate apoptosis of cancer cells, induce specific anti-cancer responses or render cancer cells more sensitive to specific chemotherapies or to radiotherapy.

Examples of such weaponized and improved vectors include: recombinant HSV-1 virus for treatment of metastatic breast carcinoma or melanoma; recombinant measles virus (MV) for treatment of myeloma and prostate cancer; recombinant Newcastle disease virus (NDV) stimulating immune system and cytokine release in liver cancer; vesicular stomatitis virus (VSV) exploiting defective interferon pathway in cancer cells; HSV-1 virus with deleted thymidine kinase gene or Ad5/3-Δ24 adenovirus modified to bind to integrins αvβ3 and αvβ5 (highly expressed on ovarian cancer cells), and which is currently being investigated in clinical trials (Kaufman et al., 2015). The immense potential of oncolytic virotherapy has been convincingly demonstrated by recombinant herpes simplex virus type 1 (HSV-1), called Talimogene laherparepvec (T-VEC) approved in 2015 for treatment of metastatic melanoma (FDA in the US, Reuters. 27 October 2015; EMA in the EU, Onclive, 2015). T-VEC efficacy is rooted in the deletion of two non-essential viral genes resulting in selective viral replication ability and promotion of regional and systemic antitumor immunity; expression of human granulocyte macrophage colony-stimulating factor (GM-CSF) allows local GM-CSF production triggering recruitment and activation of antigen-presenting cells with subsequent induction of tumor-specific T-cell responses. The drawback of T-VEC is that its efficacy against disseminated disease appears contingent upon intralesional administrations (Senzer et al., 2009; Andtbacka et al., 2015). This, rather emphatically, accentuates the rationale behind efforts to further improve systemic oncovirotherapy.

T-cell effector functions can be enhanced by delivering into tumor microenvironment certain transgenes *via* genetically engineered oncolytic viruses. Specific antigen expression on tumor cells can be combined with action of CAR-T cells expressing a receptor recognizing specifically cancer-associated antigen. Promising results were reported in preclinical studies combining CAR-T cells with oncolytic viruses armed with cytokines, chemokines, BiTEs (Bi-specific T-cell engagers), or immune checkpoint inhibitors (Guedan and Alemany, 2018; Harrington et al., 2019).

5. Immune checkpoint inhibitors and oncolytic therapy

The recent approval by the US Food and Drug Administration (FDA) of two different CAR-T cell therapies (for the treatment of leukemia and lymphoma) represents a landmark in the development of cancer immunotherapies. CAR-T cells are revolutionizing the field of cancer therapy, together with immune checkpoint blockade therapy (Guedan and Alemany, 2018).

Immune checkpoint inhibitors unblock T cell inhibitory signals and trigger antitumor T-cell responses. Checkpoint proteins targetable by therapeutic antibodies include proteins found on T cells or cancer cells, e.g. PD-1/PD-L1 and CTLA-4/B7-1/B7-2 (e.g. Russell and Peng, 2018).

Oncolytic viruses lyse tumor cells as part of viral replication cycle; by inducing changes in the tumor microenvironment ("cold" into "hot" tumor transformation) they can also increase locally the number of immune effector cells. This outcome can sensitize tumors to checkpoint inhibitors involving e.g. PD-1/PD-L1 and CTLA-4/B7-1/B7-2 molecules and/or antibodies. The effectiveness of such improved approach was demonstrated in metastatic melanoma for intralesional injections of oncolytic virus (T-VEC) and anti-PD-1 treatment (Haanen, 2017).

Administration of checkpoint inhibitors (either systemically or *via* viral transgene expression) along with oncolytic vectors has proven successful in multiple clinical and preclinical models (LaRocca and Warner, 2018; Sivanandam et al., 2019). Synergy gain could also be expected with oncolytic virus-loaded MSCs combined with immune checkpoint inhibitors. Interestingly, a novel recombinant myxoma virus construct (vPD1) designed to secrete a soluble form of PD-1 from host cells was recently reported to be able to accumulate in tumor tissue; MYXV synergy with PD-1 blockade resulted in complete response in ca. 60% of mice (Bartee et al., 2017). All these novel combination regimens will likely have a dramatic impact in the years to come.

Two clinical trials exploring oncolytic virus combination with checkpoint inhibitor stand prominently and both involve T-VEC. The trial involving combination with Ipilimumab (an anti-CTLA-4 antibody) yielded significantly higher response rates of the combination therapy arm than those of the monotherapy arm and without dose-limiting toxicities. Importantly, half of the patients demonstrated abscopal responses in distant, non-injected visceral lesions (Chesney et al., 2018). The clinical trial involving T-VEC combination with, pembrolizumab (an anti-PD-1 antibody) also yielded impressive objective response rate of 62% while in 33% of patients the response was complete. The combination therapy yielded elevated PD-L1 protein expression and increased $CD8^+$ T cells on several tumor cell subsets suggesting that oncolytic virotherapy did improve the efficacy of anti-PD-1 therapy by altering the tumor microenvironment (Ribas et al., 2017).

6. Non-systemic anticancer therapy with oncolytic virus-loaded MSCs

Use of MSCs as a non-systemic carrier of oncolytic viruses has been attempted with varying success in the therapy of glioma, colon, prostate, ovary, breast, liver and lung cancer, lymphoblastic leukemia and also in treating melanoma metastases to the brain (e.g. Stuckey and Shah, 2014; Ramírez et al., 2015; Nowakowski et al., 2016; Brittany et al., 2017; Russell et al., 2019).

The results of preclinical studies involving non-systemic administration of MSCs infected with various "armed" oncolytic viral constructs are included in Table 1.

Oncolytic herpes simplex virus (oHSV) has been among the most frequently tested in conjunction with MSCs encapsulated in biocompatible synthetic extracellular matrix (sECM). Duebgen showed that MSCs-sECM were able to support amplification of the tested oHSV-TRAIL construct (TNF-related apoptosis-inducing ligand) and triggering apoptosis in glioma cell lines nonpermissive to oHSV and resistant to TRAIL. MSC-mediated delivery could overcome the problem associated with direct oncolytic virus injection into resection cavities and negligent curative effect (Duebgen et al., 2014).

A few studies demonstrated circumvention of pre-existing anti-viral immunity and enhanced therapeutic outcomes when using oncolytic virus-infected MSCs. Mader and colleagues tested MV-infected MSCs (adipose tissue-derived) in mice bearing different orthotopic human ovarian tumor xenografts. Intraperitoneally administered virus-loaded MSCs were shown to traffic to and co-localize with the xenografts transferring measles virus infection and significantly extending survival of mice passively immunized with antimeasles antibodies (Mader et al., 2009).

Various adenoviral constructs have been extensively tested in non-systemic therapies in conjunction with MSCs. Using the syngeneic murine CMT64 lung cancer cell line to create a human adenovirus semi-permissive tumor model, Rincón et al. demonstrated the homing capacity of adenovirus-loaded murine mesenchymal stem cells (mCelyvir) to the induced tumors. A combined treatment with mCelyvir and intratumoral injections of ICOVIR5 (the adenoviral construct itself) showed synergy compared to ICOVIR5 alone. The therapeutic effects of

Table 1
Examples of preclinical anticancer therapy using MSCs as carrier for oncolytic virus.

Preclinical studies					
Tumor/host	Cell line	MSCs source	Oncolytic virus type	Route of virus-loaded MSCs administration	Reference
Glioblastoma multiforme/ SCID mice	Gli36vIII-GFl, LN229-GFl	BM-MSC	HSV	it	Duebgen et al. (2014)
Brain metastatic melanomas/ SCID, C57BL6 mice	MeWo, M12	hMSC	HSV	ica, iv	Du et al. (2017)
Lung and brain metastases/ nude, NSG mice	SK-OV-3, MDA-MB-453- EGFP	FM-MSC	HSV, R-LM249	iv	Leoni et al. (2015)
Ovarian cancer/ athymic mice	SKOV3, A2780, OVCAR5	ADSC	MV	ip	Mader et al. (2009); Mader et al. (2013)
Hepatocellular carcinoma/ SCID mice	HCC	BM-MSC	MV	iv	Ong et al. (2013)
Lymphoblastic leukemia/ SCID mice	Nalm-6	BM-MSC	MV	iv	Castleton et al. (2014)
Lung cancer and breast cancer/ NMRI nude mice	LNM35/EGF, M4A4-LM3	BM-MSC, ADSC	Adenovirus, Ad5/3	iv	Hakkarainen et al. (2007)
Pancreatic cancer/ nude mice	AsPC-1	BM-MSC	Adenovirus, Ad/RLX-PCDP	iv	Na et al. (2019)
Hepatocellular carcinoma/Balb/c athymic nude mice	HepG2	HUMSC	Adenovirus, AdAFPp-E1A and AdAFPp-E1A-122	iv	Yuan et al. (2016)
Hepatocellular carcinoma/athymic nude mice	Hep3B	BM-MSC	Adenovirus, HCC-oAd-WNTi	iv	Yoon et al. (2019)
Lung carcinoma/C57BL/6 mice	CMT64-6	BM-MSC	Adenovirus, ICOVIR5	it	Rincón et al. (2017)
Lung carcinoma, metastatic/C57BL/6J mice	CMT64-6	BM-MSC	Adenovirus, ICOVIR5	ip	Morales-Molina et al. (2018)
Ovarian cancer/ athymic nude mice, NOD-SCID mice	2e6 OVCAR8.EGFP.ffluc, OVCAR8.EGFP.ffluc	NSC	Adenovirus, CRAd-S-pk7	ip, it	Mooney et al. (2018)
Lung adenocarcinoma/ NOD scid gamma (NSG) mice	A549	MenSC	Adenovirus, ICOVIR5	ip	Barlabé et al. (2019)
Prostate cancer/ Babl/c nude mice	Ki-ras	hMSC	Adenovirus, CRAd	it	Muhammad et al. (2019)
Malignant gliomas/ Nu/nu mice	U87MG	BM-MSC	Adenovirus, CRAd	ic	Sonabend et al. (2008)
Glioblastoma multiforme/ nude mice	U87	ADSC	Adenovirus, ICOVIR17	it	Martinez-Quintanilla et al. (2015)
Colorectal cancer/Balb/c nude mice	SW620	MenSC	Adenovirus, CRAd5/F11	iv, ip	Guo et al. (2019)
Breast cancer/ CR rat (cotton rat model)	LCRT	BM-MSC	Adenovirus, CRAd-S-pk7	iv	Ahmed et al. (2010)
Metastatic breast cancer/ SCID mice	MDA-MB-231	hMSC	Adenovirus, CRAd Ad5/3.CXCR4	iv	Stoff-Khalili et al. (2007)
Glioblastoma multiforme/ athymic mice	U87MG, U251–V121	BM-MSC	Adenovirus, Δ24-RGD	ica	Yong et al. (2009)
Gallbladder cancer and glioblastoma/ CD-1 nude mice	GBC-SD, SGC-996, U251	BM-MSC	vMyx-GFP	iv, ip	Weng et al. (2014)
Glioblastoma multiforme/ athymic nude mice	U-87	ADSC	vMyx-GFP	ic	Josiah et al. (2010)

HSV – Herpes simplex virus; MV – Measles virus; vMyx-GFP – Myxoma virus,expressing green fluorescence protein; hMSC – human mesenchymal stem cells; BM-MSC – bone marrow mesenchymal stem cells; ADSC – adipose-derived stem cells; MenSC – menstrual blood-derived stem cells; HUMSC – human umbilical cord-derived mesenchymal stem cells; FM-MSC – fetal membrane mesenchymal stem cells; NSC – neural stem cells; iv – intravenous; ip – intraperitoneal; ic – intracranial; ica – intracarotid; it – intratumoral.

combined therapy were accompanied by increased tumor infiltration by recruited $CD8^+$ and $CD4^+$ T lymphocytes (Rincón et al., 2017).

Antitumor efficacy studies of syngeneic or allogeneic murine mesenchymal stem cells infected with oncolytic adenovirus ICOVIR5 (i.e. Celyvir system) have suggested that the use of both types of Celyvirs leads to higher infiltration of $CD45^+$ cells and leukocytes in the core of murine lung adenocarcinoma tumors (Morales-Molina et al., 2018).

Peritoneal cavity delivery of a conditionally replicative survivin promoter-driven adenovirus by allogeneic neural stem cells was shown to improve treatment of cisplatin-resistant ovarian metastatic tumors. The survivin promoter was used to drive the oncolytic construct since this protein is highly expressed in ovarian cancer cells (Mooney et al., 2018).

An oncolytic adenoviral construct "armed" with epidermal growth factor receptor (EGFR)-targeting bispecific T-cell engager (cBiTE) combined by Barlabé and colleagues with menstrual blood-derived mesenchymal stem cells (MenSCs) resulted in stronger anti-tumor potency of such armed ICOVIR15 construct both *in vitro* and *in vivo*, as compared to the unarmed ICOVIR15 virus (Barlabé et al., 2019).

Suppression of prostate cancer tumor growth in subcutaneous murine xenograft model was reported for intratumoral administration of human mesenchymal stem cells modified with E1 A/B adenoviral genes (necessary for viral replication) and used as carrier for replication-defective adenovirus expressing p14 and p53 or conditionally replicating oncolytic adenovirus (Muhammad et al., 2019).

CXCR4 promoter-driven conditionally replicating oncolytic adenovirus (CRAd) loaded into human mesenchymal stem cells (hMSCs) was used for intracranial treatment targeting glioblastoma, the most deadly brain tumor. Virus-loaded hMSCs were demonstrated to migrate *in vitro* and release CRAds that infected U87MG glioma cells. When injected at a distance of 5 mm anterior to the tumor site, virus-loaded hMSCs were able to migrate to the tumor site and deliver 46-fold more viral copies, as compared to the injection of adenovirus alone (Sonabend et al., 2008).

Martinez-Quintanilla et al. reported that intratumoral injections of conditionally replicating adenovirus expressing soluble hyaluronidase (ICOVIR17) mediated degradation of hyaluronic acid (HA), a component of extracellular matrix (ECM) and enhanced viral spread bringing about major antitumor effect; however, ICOVIR17 loaded into human ADSC encapsulated in biocompatible synthetic extracellular matrix (sECM-MSC) demonstrated even greater efficacy in a clinically relevant mouse model of GBM resection (Martinez-Quintanilla et al., 2015).

Studies of ADSCs infected with myxoma virus (MYXV), a promising nonhuman poxvirus candidate for oncovirotherapy demonstrated that upon intracranial administration the infected cells were able to migrate to and cross-infect experimental glioblastoma multiforme (GBM) foci, even away from the primary tumor site (Josiah et al., 2010). Subsequent study of Pisklakova and colleagues convincingly showed that MYXV knock-out construct devoid of a viral gene called M11L regulating apoptosis can trigger increased cell death in infected brain tumor-initiating cells (BTIC) which are largely responsible for deadliness of glioblastoma. Their elimination resulted in enhanced survival of immunocompetent mice burdened with BTIC-seeded glioma (Pisklakova et al., 2016). This seminal result was achieved with orthotopic delivery of the virus which only emphasizes the dormant potential of cell-mediated delivery of such myxoma construct.

Adipose tissue-derived stem cells (ADSCs) used as vaccinia virus-amplifying Trojan horse were claimed by Draganov et al., claim however that allogeneic differences associated with the induction of anti-stem cell cytotoxicity and thus allogeneic responses from both innate (NK)- and adaptive (T)- immune cells might compromise therapeutic efficacy through direct elimination of the stem cells or the induction of an anti-viral state, which can block the potential of the Trojan horse to amplify and deliver vaccinia virus to the tumor; assays detecting important patient-specific differences in the immune responses to the virus and stem cells were postulated (Draganov et al., 2019).

7. Systemic anticancer therapy with oncolytic virus-loaded MSCs

The results of preclinical studies involving systemic administration of MSCs infected with various "armed" oncolytic viral constructs are summarized in Table 1.

In order to eliminate disseminated melanoma metastases in the brain, Du and al. developed suitable models in immunocompromised and immunocompetent mice and tested the efficacy of oncolytic herpes simplex virus delivered by MSCs. Intracarotid administration of MSC-oHSV, but not of oHSV alone, effectively tracked to metastatic lesions and significantly prolonged the survival of brain tumor-bearing mice. A combination of MSC-oHSV and PD-L1 blockade in a syngeneic model increased IFNγ-producing $CD8^+$ tumor-infiltrating T lymphocytes resulted in significantly increased survival (Du et al., 2017).

A combination involving MSCs from different sources and infected with a HER2-retargeted oncolytic HSV and evaluated in two murine models of metastatic cancers following a single iv. injection of infected MSCs showed the highest concentration of carrier cells and viral genomes in the lungs. Viral genomes persisted throughout the body for at least two days. The treatment significantly inhibited growth of ovarian cancer lung metastases in nude mice and reduced by more than one-half the burden in case of breast cancer metastases to the brain in NSG mice (Leoni et al., 2015).

A study of orthotopic hepatocellular carcinoma model in SCID mice immunized with human neutralizing antibodies and treated with attenuated MV and BM-hMSCs has shown that cell-associated MVs were protected from antiviral antibodies. The authors claimed this strategy may elude immunity against MV in most of the cancer patients (Ong et al., 2013).

Human BM-MSCs were also demonstrated to efficiently deliver measles oncovirotherapy to precursor B-lineage acute lymphoblastic leukemia (ALL) cells in a xenograft model. BM-MSCs were successfully loaded with MV *ex vivo*, and MV was amplified intracellularly without signs of toxicity. Following systemic treatment 16 adults with acute lymphoblastic leukemia and receiving immunosuppressive drugs developed high-titer anti-MV antibodies (Castleton et al., 2014).

More than a decade ago MSCs loaded with oncolytic adenoviruses were demonstrated to improve the bioavailability of systemically injected oncolytic adenoviruses in orthotopic murine models of lung and breast cancer (Hakkarainen et al., 2007).

hMSCs were shown to be effective cell carriers for systemic delivery of a relaxin (RLX)-expressing oncolytic Ad (oAd/RLX) which is able to degrade dense tumor extracellular matrix of highly desmoplastic pancreatic cancer overcoming poor delivery of oAd. Complex with biodegradable polyethyleneimine-conjugated polymer enhanced the internalization of oAd into hMSC, leading to superior viral production and release from hMSCs, along with high RLX expression. Systemic administration of oAd/RLX-PCDP-treated hMSCs yielded strong antitumor effect in pancreatic tumor model due to superior viral replication (Na et al., 2019).

Application of human umbilical cord-derived MSCs (HUMSCs) was reported in eliminating postsurgical residuals and metastasis of hepatocellular carcinoma. Stem cells were loaded with a conditionally replicative adenovirus (CRAd) containing E1A gene dually regulated by α-fetoprotein promoter and microRNA-122 target sequence. Besides showing production of CRAd by differentiated HUMSCs *in vitro* Yuan et al. demonstrated hepatocyte-like transformation of HUMSC in the microenvironment of orthotopic or heterotopic hepatoma and inhibition of growth of both orthotopic and subcutaneous hepatic xenograft tumors in mice (Yuan et al., 2016).

Effectiveness of systemically delivering a hepatocellular carcinoma-targeted oncolytic adenovirus encoding Wnt-inhibiting decoy receptor sequence (WNTi) and loaded into MSCs (HCC-oAd-WNTi/MSC) was compared to control hepatocellular carcinoma (HCC)-targeted oncolytic adenovirus (HCC-oAd) shielded by mesenchymal stem cells. Intravenously injected HCC-oAd-WNTi/MSC therapeutic system homed

to HCC tumors and led to high virion accumulation in the tumors, ultimately resulting in effective growth inhibition. *In vitro* oncolysis of HCC cells was demonstrated under both normoxic and hypoxic conditions confirming HCC-oAd-WNTi hypoxia responsiveness (Yoon et al., 2019).

Engineered chimeric oncolytic adenoviruses were also used in studies targeting colorectal tumor cells with menstrual blood-derived MSCs. Such adenoviruses indeed accumulated in colorectal tumors and mediated marked inhibitory effects (Guo et al., 2019).

Owing to suppressed production of interferon-γ (IFN-γ) by activated T cells, an improved delivery, enhanced dissemination and increased persistence of adenovirus delivered by MSCs was observed in a breast fibrosarcoma model when compared to virus administration alone (Ahmed et al., 2010).

In testing therapeutic strategies for metastatic breast cancer, the effectiveness of homing to the tumor site and extended animal survival were compared between intravenous injections of conditionally replicating Ad (CRADs) loaded into hMSCs and CRAd alone using the MDA-MB-231 murine pulmonary breast metastasis model (Stoff-Khalili et al., 2007).

A significant therapeutic effect obtained in systemic treatment of gallbladder carcinoma (GBC) was observed using human BM-MSCs infected with myxoma virus (MYXV), almost matching intratumoral injections of MYXV. This demonstrated MYXV to be effectively delivered by MSCs to sites distant from the injection site, making intravenous injection of MYXV a possible therapeutic approach in treating GBC tumors (Weng et al., 2014).

Improved survival and eradication of glioma was reported for Delta-24-RGD adenoviral construct loaded into GFP-labeled hMSCs and delivered into intracarotid artery of mice harboring orthotopic U87MG or U251–V121 xenografts *via* infection of human glioma and release of Delta-24-RGD improving survival and tumor eradication (Yong et al., 2009). This demonstrated that glioma can be successfully targeted systemically. Myxoma virus was also capable of restoring apoptosis in brain tumor initiating cells (BTIC) by transfer of a knockout construct devoid of M011L viral gene that regulates apoptosis (Pisklakova et al., 2016). Although this result was not achieved *via* systemic administration with MSCs, attempts at systemic delivery using this construct are now underway in our laboratory.

8. Limitations of MSC use in systemic therapy

One of the barriers encountered by oncolytic viruses upon intravenous administration (as for any other viruses), is the host response: circulating antibodies, cytokines, complement proteins and immune cells in the bloodstream eliminate the viral particles; those that manage to reach particular organs are then scavenged by immune system cells. This largely explains the generally ineffective outcome of intravenous delivery of unshielded virus and tumor tissue targeting (Fig. 1.). This is especially crucial when contemplating virotherapy of disseminated or hard-to-reach tumor sites. In the case of intratumoral administration, even though anti-viral response from the immune system is diminished, the immunosuppressive tumor microenvironment still can drastically limit replication of the therapeutic oncolytic construct. Thus, the ideal systemic cell carrier should be easily infected *ex vivo* by the therapeutic oncolytic virus, without being overly permissive, i.e. without cytotoxicity profile preventing transit of the therapeutic agent to target) yet allowing replication of progeny virus to infect targeted cancer cells (Harrington et al., 2019).

MSCs have been extensively reported as carriers for oncolytic viruses providing them with effective shield against neutralizing host effects and targeting them to tumor sites (e.g. Bosu and Kiperos, 2008; Willmon et al., 2009; Shi et al., 2010; Josiah et al., 2010; Sensebé and Fleury-Cappellesso, 2013; Zhao et al., 2015; Leoni et al., 2015; Aurelian, 2016).

Some researchers have raised, nonetheless, the issue of limited persistence of MSCs upon systemic injection and, actually, low efficiency in targeting damaged/inflamed tissues (Lee et al., 2009; von Bahr et al., 2012; Ranganath et al., 2012).). Poor expression of adhesion or homing ligands responsible for inflammation site homing can be negatively affected during *in vitro* expansion of MSCs (Wu and Zhao, 2012; Hocking, 2015). Enhanced homing of MSCs to inflammation sites, can be engineered by conjugating specific antibodies or by other approaches such as triggering transient overexpression of CD44, the hyaluronic acid (HA) receptor (Corradetti et al., 2017). Other therapeutic approaches to enhance systemic delivery of MSCs include: engineered hyaluronidase-mediated degradation of extracellular matrix (ECM), ultrasound cavitation or temporal vasodilation enhanced viral delivery (Martinez-Quintanilla et al., 2015; Harrington et al., 2019). Conversely, blocking CD44 with antibodies or engineering CD44 on the MSC membrane should reduce homing of intravenously administered MSC to inflammatory sites.

Intravenous administration of cell-shielded oncolytic viruses is not a very invasive procedure, whereas local injections in some instances can be difficult to achieve. Lung capillaries can form, however, a first-pass barrier for MSCs because of their size. Although this might be beneficial for treating certain medical conditions (e.g. oncolytic therapy of lung neoplasia) it could also be a barrier for systemic therapy of peripheral tumors (Fischer et al., 2009). Intravenous administration of MSCs leads to strong initial accumulation in the lungs (Gholamrezanezhad et al., 2011). Adhesion molecules on capillary endothelium probably contribute to retention of MSCs in the lung; blocking CD49d decreases the number of lung-trapped MSCs (Nystedt et al., 2013). Interestingly, adhesion of MSCs to lung endothelium can be attenuated by treatment with pronase following which they are found elsewhere in greater numbers (Kerkelä et al., 2013).

The first-pass problem with intravenous administration could perhaps be solved or reduced by intraarterial infusion of MSCs. This procedure avoids the first-pass lung retention effect and results in decreased accumulation of MSCs in lungs (Walczak et al., 2008; Mäkelä et al., 2015), thus legitimizing this procedure when trying to achieve improved targeting of tissues in peripheral locations. Available data suggest that intraarterial administration of MSCs contributes to tissue biodistribution and bioavailability of MSCs in clinically relevant settings. This might have important implications for treating pathologies such as gliomas, for example. It has been shown that delivery of MSCs through the internal carotid artery facilitates their migration and homing into injured brain areas compared with administration *via* the femoral vein (Nakamizo et al., 2005; Walczak et al., 2008; Doucette et al., 2011).

Improvements in engineering of viral constructs and MSCs, coupled with the “Trojan horse” concept has led to a wealth of novel therapeutic possibilities. With precautions and barriers to overcome, MSC-mediated delivery could become a promising therapeutic delivery platform.

9. MSC-mediated oncolytic virotherapy - clinical studies

There have been a few clinical studies combining the use of various MSCs and oncolytic viruses (see Table 2).

The first clinical study (EudraCT Number: 2008-000364-16) was based on an exploratory study (García-Castro et al., 2010) using CELYVIR (autologous MSCs infected with ICOVIR-5, a modified adenovirus with replication restricted to cells with an activated RB pathway) to treat metastatic neuroblastoma and other pediatric refractory malignancies (Ewing's sarcoma with bone or bone marrow metastases, metastatic osteogenic sarcoma, metastatic soft tissue sarcoma, metastatic rhabdomyosarcoma) as well as on a more detailed study (see: Melen et al., 2016). The clinical study was prematurely ended and no results seem available.

Another study with CELYVIR, NCT 01844661 (Phase I) also made use of bone marrow-derived autologous mesenchymal stem cells infected with ICOVIR-5 for systemic treatment of metastatic solid tumors

Table 2
Clinical trials of anticancer therapy using MSCs as carrier for oncolytic virus.

Clinical studies					
Clinical trial (status)	Tumor	MSC source	Oncolytic virus type	Route of virus-loaded MSCs administration	Reference
EudraCT Number: 2008-000364-16 CELYVIR (ended prematurely)	Pediatric patients with refractory or recurrent solid tumors	BM-MSC	Adenovirus, ICOVIR5	iv	García-Castro et al. (2010); Melen et al. (2016)
NCT 02068794 (ongoing)	Ovarian cancer	ADSC	Measles virus (MV-NIS)	ip	Mader et al. (2013)
NCT 01844661; CELYVIR (completed)	Metastatic and refractory tumors	BM-MSC	Adenovirus, ICOVIR5	iv	Ramírez et al. (2015)
EudraCT Number: 2019-001154-26 AloCELYVIR (ongoing)	Relapsed or refractory extracranial solid tumors	BM-MSC	Adenovirus, ICOVIR5	iv	n/a
NCT03896568 (ongoing)	Recurrent high-grade glioma	BM-MSC	Adenovirus, DNX-2401	ia	Kiyokawa and Wakimoto (2019)
NCT0307213 (ongoing)	Newly diagnosed glioblastoma, astrocytoma	NSC	Adenovirus, CRAd-survivin-pk7	icv	Kiyokawa and Wakimoto (2019)

BM-MSC – bone marrow mesenchymal stem cells; ADSC – adipose-derived stem cells; NSC – neural stem cells; iv – intravenous; ip – intraperitoneal; ia – intraarterial; icv – intracavitary n/a – not available; MV-NIS – measles virus encoding thyroidal sodium iodide symporter; CELYVIR – bone marrow-derived autologous MSCs infected with ICOVIR5 (adenoviral construct); AloCelyvir – allogeneic bone marrow-derived autologous MSCs infected with ICOVIR5; DNX-2401 – adenovirus with integrin binding RGD-4C motif; CRAd-survivin-pk7 - conditionally replicative adenovirus with survivin promoter and fiber-modified with polylysine.

in children and adults; the study was completed in 2016. The combination of MSCs and oncolytic adenovirus was found to be safe warranting further evaluation in the phase II setting. No further information is available.

The NCT 02068794 trial is a phase I/II study of side effects and best dose of intraperitoneal administration of adipose tissue-derived mesenchymal stem cells (ADSC) infected with oncolytic measles virus encoding thyroidal sodium iodide symporter (MV-NIS); the trial is set for recurrent ovarian cancer patients. The study is ongoing.

Yet another study exploring ICOVIR-5 is EudraCT Number 2019-001154-26 in which allogeneic BM-MSCs have been used (AloCELYVIR); it is a feasibility trial of the combination of AloCELYVIR with chemotherapy and radiotherapy used to treat children and adolescents with relapsed or refractory extracranial solid tumors. The study is ongoing.

Another study involving administration of allogeneic bone marrow-derived human mesenchymal stem cells loaded with oncolytic virus is NCT03896568; in this instance carrier BM-hMSCs are infected with DNX-2401, an oncolytic adenovirus with integrin binding RGD-4C motif (Delta-24-RGD); the therapeutic construct is administered by transfemoral super-selective endovascular intracranial injection (i.e. intraarterial) to patients with recurrent glioblastoma (GBM), gliosarcoma or wild-type IDH-1 anaplastic astrocytoma.

Also neural stem cells loaded with construct have been explored in a clinical setting (NCT03072134) to deliver CRAd-survivin-pk7 a conditionally replicative oncolytic adenovirus with survivin promoter and fiber-modified with polylysine (Kiyokawa and Wakimoto, 2019).

10. Future directions

Even though the preclinical studies are highly promising, effectiveness of oncolytic virotherapy remains suboptimal, with only a fraction of patients undergoing complete tumor regression (called “elite responders”) but the majority still do not (Bell and McFadden, 2014). Effectiveness of virotherapy ultimately relies on eliminating factors that impede efficient virus delivery to the target sites, particularly for disseminated cancer burden (e.g., insufficient numbers of tumor-penetrating viral particles) (Marchini et al., 2016).

Future advances in oncolytic virotherapy will likely come from engineered viral constructs and their increasingly sophisticated carriers: transgene-armed oncoviral platforms interfering with host cellular defenses (e.g. by manipulating cellular DEAD box RNA helicases (e.g. Rahman et al., 2017) or allowing regulation of intracellular signaling pathways restoring apoptosis (e.g. in brain tumor initiating cells, see Pisklakova et al., 2016), or focusing on some highly overexpressed targets (such as interleukin 13 and ephrin receptors in glioblastoma) with ligand-cytotoxic agent combination warheads or encapsulating carrier cells infected with oncolytic viruses in synthetic extracellular matrices that would allow prolonged release of therapeutic agents (Kauer et al., 2012).

As of the end of 2019, therapy of the deadliest cancers continues to be a challenge although breakthroughs seem to be within reach. Still, for systemic oncolytic virotherapy there remains a stern firewall: effective delivery. Smart cellular carriers, including engineered MSCs, stand a good chance to become the platform allowing authorized access of viral oncolytics to metastatic lesions through this firewall.

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